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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,733	11/08/1999	ALPHONSE GALDES	CIBT-P02-052	5606

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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	20

DATE MAILED: 02/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/435,733	Galdes et al.
Examiner	**Art Unit**
Michael Brannock, Ph.D.	1646

-- The MAILING DATE of this communication appears on the cover sheet with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 20, 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-7 and 9-58* is/are pending in the applica

4a) Of the above, claim(s) *see attached* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *see attached* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 19, 12/17/01, have been entered in full.

2. Claims 1-7, 9-58 are pending.

3. Claims 12, 24-29, 32-40, 42, 43, and 49 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, as set forth in Paper 18, 8/15/01. Additionally, as set forth in Paper 18, claims 1-7, 9-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50-58 will be examined only to the extent that the claims are directed to methods of treatment of diabetic neuropathy comprising the administration of a sonic hedgehog polypeptide, as per Applicants' election in Paper 17. It is noted that claim 49 is included in Group I but does not encompass the elected species, and are therefore withdrawn from consideration.

Withdrawn Rejections/Objections:

4. The objections to the specification, as set forth in item 4 of Paper 18, are withdrawn in view of Applicant's amendments.

5. The rejection of Claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 under 35 U.S.C. 101, as set forth in item 6 of Paper 15, is withdrawn in view of Applicants' amendments put forth in Paper 18.

6. The rejection of claims 1-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50 and 51 under 35 U.S.C. 112, second paragraph, as set forth in item 8 of Paper 15, is withdrawn in view of Applicants' amendments put forth in Paper 18.

Maintained Rejections:

7. Claims 1-7, 9-11, 13-23, 30, 31, 41, 44, 45-47, 48, 50-58 stand rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 10 of Paper 18 and for the additional reasons below. The specification, while being enabling for methods of treating and protecting against cisplatin and taxol induced neuropathy and a neuropathy resulting from sciatic nerve crush, or viral induced neuropathy comprising the systemic administration of sonic hedgehog polypeptide, does not reasonably provide enablement for the treatment for or protection against other neuropathies, nor for the treatment of any neuropathy comprising the systemic administration of a hedgehog agonist other than a polypeptide 100% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

Applicant's amendments, put forth in Paper 18, have limited the scope of the claimed treatment methods to systemic administration of a hedgehog agonist. The specification presents the results obtained in several experimental neuropathic models, wherein sonic hedgehog is systemically administered (subcutaneous (s.c.) administration). Systemic administration of

Sonic hedgehog appeared to be effective in several of the models, e.g. cisplatin and taxol induced neuropathy (page 24) and rat sciatic nerve crush injury (page 79). However, in the other cases, it is unclear if administration of sonic hedgehog has a measurable beneficial effect. In the example of the SOD deficient mice no significant differences were found after treatment of male mice (page 77, l0). Further, in the galactose model of neuropathy, it is unclear if any difference between the groups is significant (Figure 23). Additionally, treatment of diabetic rats with sonic hedgehog does not appear to have been attempted. Thus, it is unclear based on the teachings of the specification, which of the multitude of neuropathic disorders contemplated are amenable to treatment with sonic hedgehog or any other hedgehog agonist.

The claims are now limited to treatment methods comprising systemic administration of a hedgehog agonist. Subsequent to the filing of the instant application, several groups, including one of the instant inventors, reported limited success with systemic administration of sonic hedgehog in the treatment of peripheral neuropathies. Welty et al., *Soc. Neurosci. Abs.* 27(2)pp2621, 2001, report that systemic administration of sonic hedgehog did not alter the disease course in transgenic ALS mice. Further, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog for the treatment of peripheral neuropathies, only certain neuropathies are amenable to treatment (e.g ALS is not) and of those that are (e.g. sciatic nerve crush), the specificity of the hedgehog agonist is critical, e.g. sonic and desert hedgehog are

80% identical, yet sonic hedgehog is effective in the treatment of sciatic nerve crush whereas desert hedgehog is not.

Thus, it is unclear which of the multitude of neuropathic disorders contemplated are amenable to systemic treatment with sonic hedgehog or any other hedgehog agonist, and of those that are amenable to treatment with sonic hedgehog, it is unclear what other hedgehog agonists could be used systemically.

As set forth previously, Oppenhiem *et al. Mol. Cell. Neuroscience* 13(348-361)1999 reported mixed results with the administration of sonic hedgehog in the treatment of a variety of different neuronal populations. Oppenhiem *et al.* report that the administration of exogenous sonic hedgehog to embryos *in vivo* or to motor neuron cultures failed to promote the survival of several different neuronal population including spinal motor neurons, spinal interneurons, sympathetic preganglionic neurons, sensory neurons and neuronal precursors (see the Abstract). Further, Oppenhiem *et al.* were "surprised to discover that Shh failed to promote the survival of chick embryo spinal chord cells and actually induced the death of apparent neuronal and floor-plate cells during the first stage of spinal chord programmed cell death" (see page 353, col. 2). Thus, it is unclear which types of neuropathies are amendable to treatment. The specification has merely provided to the skilled artisan an invitation to begin further research and investigation into which other of the multitude of pathologies involving the motor and/or sensory nervous systems could ultimately be treated as claimed; and then to begin further research and investigation into the particular methodologies of administration and treatment schedule that

would be required once and amendable disorder has been identified. The specification has provided no guiding principle to identify which particular neuropathies would be amendable to treatment, and nor is such a principle known in the art. The skilled artisan is therefore left to undergo extensive random trial and error experimentation in order to determine which neuropathologies are amendable to treatment.

Applicant argues that the specification has provided several working examples and that it would not require undue experimentation to determine which other neuropathies are amendable to treatment; applicant adds that the presence of inoperative embodiments within the scope of the claim does not necessarily render a claim nonenabled. This argument has been fully considered but not deemed persuasive. As set forth previously, Applicant's enabled disclosure is not commensurate with the scope of the claims, wherein the skilled artisan is therefore left to undergo extensive random trial and error experimentation in order to determine which neuropathologies are amendable to treatment.

Applicant argues that Applicants cannot be expected to wait for laboratory animals to spontaneously develop neuropathy to test the claimed methods in every potential cause of peripheral neuropathy. This argument has been fully considered but not deemed persuasive because such a requirement has not been set forth. The issue is that the effects of hedgehog agonists on the peripheral nervous system are extremely complex and unpredictable, as evidenced by Oppenhiem et al.; and the specification has provided no guiding principle to identify which particular neuropathies would be amendable to treatment, and nor is such a

principle known in the art. The skilled artisan is therefore left to undergo extensive random trial and error experimentation in order to determine which neuropathologies are amendable to treatment.

Applicant argues that the determination of enablement must be made on an evaluation of the evidence as a whole; and the examiner's reliance on Oppenhiem *et al.* constitutes an unfair picking and choosing of references. This argument has been fully considered but not deemed persuasive. Oppenhiem et al. is fairly representative of the enormous body of literature available to the artisan which establishes the complexity and unpredictability of the effects of hedgehog polypeptides on the nervous system. Applicant further argues that the differences between the model system used by Oppenheim et al. and that of the instant Application make the Oppenheim et al. reference irrelevant to the claimed subject matter. For support of this assertion, Applicant points to a discussion in the Oppenheim et al. reference concerning the work of Miao et al., *J. Neuroscience* 17(5)5891-5899, 1997, wherein Oppenheim et al. state "In view of the report that Shh can promote the survival of cultured rat embryo spinal interneurons (Miao et al., 1997), the present negative results with chick embryo interneurons were, on the face of it, unexpected. However, unlike rat and mouse embryos, spinal interneurons in the chick represent one of the few neuronal population in which PCD of postmitotic cells does not occur naturally. Therefore, it is perhaps not surprising that interneuron numbers were unaffected by Shh." Thus Applicant concludes that although Oppenheim et al. present seemingly contradictory evidence, the differences between the anatomy of their system and mammalian neural anatomy make any

comparisons between their work and Applicant's work tenuous, especially when corroborative evidence using mammalian systems exists. Applicant further urges that the spinal interneurons studied by Oppenheim et al. are not the ultimate mediators of peripheral neuropathy, and are distinct phenotypically from the neurons that degenerate in peripheral neuropathy.

This argument has been fully considered but not deemed persuasive for the following reasons. In the passage of the Oppenheim et al. discussion pointed to by Applicant, Oppenheim et al. is contrasting the effects of hedgehog polypeptides on spinal interneurons in chick and mice, however Applicant appears to be ignoring the content of the rest of the discussion which involves the other spinal chord cell types studied, including spinal motor neurons, and also sympathetic preganglionic neurons, and sensory neurons (see page 359 and also The Abstract), see also page 9, lines 7-10 of the previous Office action. Moreover, far from corroborating Applicant's position, in the mouse model of Miao et al., pointed to by Applicant, Miao et al. found that "neurons of the peripheral nervous system show no survival in response to sonic hedgehog administration" (see page 5898, col 1, 2nd and 3rd paragraphs, of Miao et al.).

Additionally, the specification has provide results with the administration of the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide, PEGylated or as a fusion with an immunoglobin (pg 79) yet the claims encompass the administration of any compound that is encompassed by the definition of a hedgehog agonist, i.e., any compound "which mimics or potentiates the activity of a wild-type hedgehog protein" (see page 10, lines 24-26). As set forth previously, it is well appreciated that the activities of patched (and therefore of hedgehog)

are extremely complex and as yet controversial and incompletely identified (see *Stull and Iacovitti, Experimental Neurobiology* 169(1)36-43, 2001, especially page 40); the claims, therefore, encompass treatments involving the systemic administration of compounds which alter any aspect of hedgehog signaling. However, there appears to be no disclosure of such molecules, nor guidance as to how to produce such a molecule, nor is such a molecule known in the art. The claims claim a process using such a molecule, yet the specification appears to offer no guidance other than an invitation to the skilled artisan to perform random trial and error experimentation to try to find such a molecule (see page 48-49 for example), if such a molecule can be found. Further, the art is equivocal about the role of hedgehog signaling pathways in the development and/or maintenance of neural tissue. The results of *Stull and Iacovitti, Experimental Neurobiology* 169(1)36-43, 2001 suggest that sonic hedgehog does not signal through either PKA, IP-3K/PKC or DA signal transduction pathways (see page 40 first paragraph) and that activation of PKA does not inhibit sonic hedgehog induction of neurons (see page 40, 2nd col. 1st paragraph). Further, the effects of hedgehog polypeptides on motor and sensory neurons are unpredictable and sometimes contrary to what would be needed for a therapy, e.g. *Oppenheim et al*, discovered that sonic hedgehog can actually induce neuron cell death, and that altered concentrations of sonic hedgehog induce aberrant phenotypes that are removed by programmed cell death (see the Abstract) - thus adding to the complexity and uncertainty involved in the use of sonic hedgehog on neural tissues. Additionally, as set forth above, in the art of systemic hedgehog administration, to which the claims have now been limited, the suitability of a given

hedgehog agonist for a given treatment is dependent, in some unknown way, on the chemical identity of the agonist, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog and not desert hedgehog is effective in the treatment of sciatic nerve crush, see Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000.

Applicant argues that the specification provides a detailed description of a small molecule hedgehog agonist, e.g. PKA inhibitors, and that the specification teaches the use of a high through-put screen for the identification of such molecules. This argument has been fully considered but not deemed persuasive. As set forth above, it would require undue experimentation on the part of one highly skilled in the art to try to find agonists other than sonic hedgehog for systemic administration for the treatment of peripheral neuropathies, see Engber et al., show that desert hedgehog is not useful for the treatment of sciatic nerve crush and *Stull and Iacovitti, Experimental Neurobiology* 169(1)36-43, 2001 who suggest that sonic hedgehog does not signal through either PKA, IP-3K/PKC or DA signal transduction pathways (see page 40 first paragraph) and that activation of PKA does not inhibit sonic hedgehog induction of neurons (see page 40, 2nd col. 1st paragraph). The instant specification provides to the skilled artisan only an invitation to perform research and investigation to try and find agonists of hedgehog that are useful in treating peripheral neuropathies. Only the desired function and assays to measure the function of the agonist are taught in the specification. However, as the skilled artisan readily appreciates, a simple wish for a compound with a particular function is not adequate guidance to produce that compound.

Applicant argues that Stull and Iacovitti, cited by the examiner, is not applicable to the present invention, primarily because none of the experiments of Stull and Iacovitti examine the effects of Shh administration in the absence of FGFs. This argument has been fully considered but not deemed persuasive. Applicant's attention is drawn to page 39, first paragraph of RESULTS, wherein Stull and Iacovitti discuss the results of experiments wherein Shh alone or in combination with FGF is added to the explants.

Applicant concludes that the efficacy of the prophetic embodiments of the invention can be readily evaluated by one of skill in the art without undue experimentation. This argument has been fully considered but not deemed persuasive for the many reasons discussed above. Additionally, Applicant has provided no post filing date evidence in support of this contention so that the examiner can evaluate it.

8. Claims 1-8, 10, 11, 13, 14, 16-23, 30, 31, 41, 44, 45-47, 48, 50-58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and for the additional reasons discussed below.

Applicant argues that one of skill in the art would have been able to recognize which compounds are hedgehog agonists. Applicant argues that sufficient guidance is provided to identify these compounds. This argument has been fully considered but not deemed persuasive.

The claims require *in vivo* methods of preventing dysfunction and/or degradation of functional performance of motor or sensory nerves comprising systemically administering a "therapeutic amount" or an "effect amount" of a hedgehog agonist. The specification describes many molecules that are asserted to be hedgehog agonists, however one skilled in the art would not know which, if any, other than sonic hedgehog has the property of being efficacious for systemic administration in the treatment of peripheral neuropathies. There appears to be no description of such a molecule, nor guidance as to what structural characteristics such a molecule might possess, nor is such a molecule known in the art. Nor has the specification put forth what structural characteristics a compound is required to have in order to function within the definition of "hedgehog agonist" and to be effective for systemic administration in the treatment of peripheral neuropathies, and, yet, also be structrually different than sonic hedgehog. As discussed above, Engber et al., *Soc. Neurosci. Abs.* 26(1-2)Abs No. 792.14, 2000, report that systemic administration of sonic hedgehog, but not desert hedgehog, improved functional recovery following sciatic nerve crush. Thus, it appears that, in the art of systemic administration of hedgehog in the treatment of peripheral neuropathies, only certain neuropathies are amenable to treatment (e.g ALS is not) and of those that are (e.g. sciatic nerve crush), the specificity of the hedgehog agonist is critical, e.g. sonic and desert hedgehog are 80% identical, yet sonic hedgehog and not desert hedgehog is effective in the treatment of sciatic nerve crush. Applicant has not provided a guiding principle to allow one skilled in the art to know which hedgehog agonist, other than sonic hedgehog, are effective in treating any peripheral neuropathy.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-4, 6, 7, 9-11, 13-18, 21, 30, 31, 41, 44-48, and 50-58 under 35 U.S.C. 102(b) as being anticipated by WO 95/18856, Ingham et al., 13 July 1995, as set forth previously in item 8 of Paper 18.

Applicant argues that the relationship between the present claims and the cited art is largely analogous to the situation of *Corning Glass Works v. Sumitomo Electric USA*, e.g. that the presently claimed invention is a species which is unobvious and patentable over the generic teachings of Ingham et al.. Applicant further urges that prior to Applicant's disclosure, one of skill in the art could not have reasonably anticipated that systemically administered polyeptides would be effective in the treatment of peripheral neuropathies and that there is no motivation in the Ingham et al. disclosure to select systemic administration to treat peripheral neuropathies.

This argument has been fully considered but not deemed persuasive. At page 63, lines 15-20, Ingham et al. specifically teach systemic administration of the polypeptides, e.g. intravenous and subcutaneous administration, and directly contrast these routes with those used

to treat neuropathies of the central nervous system to which intraventricular and intrathecal injection are recommended. Thus, one of ordinary skill in the art would clearly understand that Ingham et al. teach systemic administration of hedgehog polypeptides for the treatment of peripheral neuropathies, e.g. virally induced peripheral neuropathy, and neuropathies induced by metabolic disease (idiopathic), or those associated with age, e.g. cardiac arrhythmia (see page 57).

11. Claims 1-4, 6, 7, 9-11,13-18, 21, 30, 31, 41, 44-48, 50-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, in view of Porter JA *et al., Science* 274(255-259)1996, as set forth in item 15 of Paper 18.

Applicant's arguments are based on the alleged impropriety of the Ingham et al. reference against the claims. These arguments have been fully considered, discussed above, and deemed unpersuasive.

Claims 1-4, 6, 7, 9-11,13-21, 23, 30, 31, 41, 44-48, 50-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, in view of Pepinsky RB *et al., J. Biol. Chem.* 273(22)14037-14045, 1996, as set forth on page 15 of Paper 18.

Applicant's arguments are based on the alleged impropriety of the Ingham et al. reference against the claims. These arguments have been fully considered, discussed above, and deemed unpersuasive.

12. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 95/18856, Ingham et al., 13 July 1995, in view off WO 96/29342, Jonassen et al., 26 Sep. 1996, as set forth in item 16 of Paper 18.

Applicant's arguments are based on the alleged impropriety of the Ingham et al. reference against the claims. These arguments have been fully considered, discussed above, and deemed unpersuasive.

Conclusion

13. No claims are allowable.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

February 6, 2002

YVONNE EYLER, PH.D
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